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Published in:
Journal of genetic counseling

DOI:
10.1002/jgc4.1206
10.1002/jgc4.1206

Publication date:
2020

Received: 20 March 2019 | Revised: 17 October 2019 | Accepted: 3 December 2019

DOI: 10.1002/jgc4.1206

ORIGINAL ARTICLE

National Society of Genetic Counselors | WILEY

How to inform at-risk relatives? Attitudes of 1379 Dutch patients, relatives, and members of the general population

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Funding information
We acknowledge the Dutch Association of Clinical Geneticists (VKGN) and the 'Stichting Kwaliteitsgelden Patiënten Consumenten' (SKPC) for their financial support. In addition, we acknowledge the financial support from the Netherlands Cardiovascular Research Initiative: an initiative with support of the Dutch Heart Foundation, CVON2015-12 eDETECT.

Abstract

The uptake of predictive DNA testing in families with a hereditary disease is <50%. Current practice often relies on the proband to inform relatives about the possibility of predictive DNA testing, but not all relatives are informed adequately. To enable informed decision-making concerning predictive DNA testing, the approach used to inform at-risk relatives needs to be optimized. This study investigated the preferences of patients, relatives, and the general population from the Netherlands on how to inform relatives at risk of autosomal dominant diseases. Online surveys were sent to people with autosomal dominant neuro-, onco-, or cardiogenetic diseases and their relatives via patient organizations (n = 379), and to members of the general population via a commercial panel (n = 1,000). Attitudes of the patient and population samples generally corresponded. A majority believed that initially only first-degree relatives should be informed, following the principles of a cascade screening approach. Most participants also thought that probands and healthcare professionals (HCPs) should be involved in informing relatives, and a large proportion believed that HCPs should contact relatives directly in cases where patients are unwilling to inform, both for untreatable and treatable conditions. Participants from the patient sample were of the opinion that HCPs should actively offer support. Our findings show that both patients and HCPs should be involved in informing at-risk relatives of autosomal dominant diseases and suggest that relatives' 'right to know' was considered a dominant issue by the majority of participants. Further research is needed on how to increase proactive support in informing of at-risk relatives.

KEYWORDS

attitudes, autosomal dominant disease, beliefs, cascade screening, cascade testing, communication, ethics, family, genetics services, inherited predisposition, population perspectives, service delivery models, survey design

1 | INTRODUCTION

In hereditary diseases with an autosomal dominant inheritance pattern, which includes the majority of hereditary cardiac, oncological, and neurological diseases, first-degree relatives are at 50% risk of carrying the genetic predisposition (Miller, Wang, & Ware, 2013). Predictive DNA testing is possible for at-risk relatives when a pathogenic variant is identified in the proband (the first affected person in the family in whom a DNA test is performed). It is important to allow genotype-positive relatives to participate in preventive management strategies when available (Miller et al., 2013). Predictive DNA testing also allows at-risk relatives to make informed decisions regarding life choices and to consider their reproductive options in case of a child wish. Genotype-negative relatives can be reassured about disease risk in themselves and their offspring (Miller et al., 2013).

In current Dutch practice, the genetic counselor asks the proband in whom a pathogenic variant is identified to inform relatives about the possibility of predictive DNA testing. This is referred to as the 'family-mediated' approach (Christiaans, Birnie, Bonsel, Wilde, & van Langen, 2008; Leenen et al., 2016). This family-mediated approach is also described in previous research conducted in other, Western countries (Godard, Hurlimann, Letendre, & Egalite, 2006; Schwiter, Rahm, Williams, & Sturm, 2018). Depending on the country and clinic, the genetic counselor can provide a family letter to help probands inform at-risk relatives (Burns, Ingles, & James, 2018; Christiaans et al., 2008; Leenen et al., 2016; Menko et al., 2013; Young et al., 2019; Dheensa, Lucassen, & Fenwick, 2018). Previous research indicates that relatives generally appreciate being informed by someone from their family, as this is the most personal and logical approach (Whyte, Green, McAllister, & Shipman, 2016; Wiseman, Dancyger, & Michie, 2010). However, previous studies have only been performed in probands and relatives attending genetic counseling. Uptake studies in onco- and cardiogenetic diseases found that about half the relatives attend genetic counseling, specifically 53% in women and 12% in men in BRCA1/2 in the UK (Brooks et al., 2004), 39% in hypertrophic and dilated cardiomyopathy (Miller et al., 2013) and 60% in long QT syndrome in Australia (Burns, McGaughran, Davis, Semsarian, & Ingles, 2016), and 39% in hypertrophic cardiomyopathy (Christiaans et al., 2008) and 57% in different inherited cardiac diseases in the Netherlands (Van der Roest, Pennings, Bakker, van den Berg, & van Tintelen, 2009). A systematic review of Menko et al. (2018) on uptake in hereditary cancers showed that uptake rates ranged from 21% to 44% for hereditary breast and ovarian cancer, and 41 to 94% in Lynch syndrome, based on reports of genetic centers in different countries. This suggests that some relatives are not adequately informed or not informed at all. This was recently illustrated by a legal case in the United Kingdom, in which relatives were not informed about the hereditary disease in their family. This case questioned the duty of healthcare professionals (HCPs) to inform at-risk relatives (Lucassen & Gilbar, 2018).

Considering the low uptake of genetic counseling and predictive DNA testing, researchers from different countries proposed a more active role for HCPs in the information process in which HCPs have direct contact with relatives (Aktan-Collan et al., 2007; Menko et al., 2018; Sermijn et al., 2016; Suthers, Armstrong, McCormack, & Trott, 2006). However, more active approaches to inform relatives have seldomly been used in patient care. In Denmark, a direct contact approach is used for contacting at-risk relatives by the national Hereditary Nonpolyposis Colorectal Cancer (HNPCC) register, showing support by 78% of relatives and 82% of the general population (Petersen et al., 2019). In the past, a direct contact has been used in the Netherlands in familial hypercholesterolemia as part of a temporary national screening program (Van Maarle, Stouthard, Marang-Van de Mheen, Klazinga, & Bonsel, 2001). However, using more active approaches raises questions regarding psychological, legal, and ethical issues: Would direct contact cause psychological harm in relatives and harm to family relationships? Do HCPs have a duty to warn at-risk relatives? How can we respect the right not to know? How do the right not to know and the right on privacy conflict with the duty to warn, and how should we handle this?

To our knowledge, there have only been a few quantitative studies that have assessed the attitudes of patients and relatives regarding how they prefer at-risk relatives to be informed and how these ethical issues should be handled on group level, and these studies were often part of larger studies on attitudes toward genetic testing (Gilbar et al., 2016; Leenen et al., 2016). None of these studies included members of the general population. Attitudes of the general population are specifically of interest as they are a proxy for relatives unaware of a hereditary disease in their family and can help us explore the opinions of relatives who do not attend genetic counseling. Incorporating the attitudes and preferences could improve the approach used to inform at-risk relatives.

This survey study aimed (a) to assess the preferences for how at-risk relatives should be informed, and by whom, and (b) to investigate attitudes regarding ethical issues related to informing at-risk relatives. By asking both the patient population and the general population from the Netherlands to participate, we could compare their attitudes regarding their approach used to inform at-risk relatives. This study was conducted to inform a Dutch clinical guideline on informing at-risk relatives of hereditary diseases.

2 | METHODS

2.1 | Participants

Two groups of participants were asked to fill out a survey: (a) a Dutch patient sample of adult patients with an autosomal dominant neurological, oncological, or cardiac disease and adult first- and further-degree relatives of patients with such a disease, including relatives who carry the genetic variant and relatives who do not; and (b) a Dutch general population sample of adults in the general population without a known hereditary disease themselves or in their family.

Participants with a hereditary disease themselves or in their family were asked to fill out the survey via Dutch patient organizations (see Supplementary Material S1). Members of the

general population were asked to participate using a Dutch online commercial survey panel focused on health research questions (FlyCatcher, 2019). The panel members, participants who agreed to take part in FlyCatcher surveys, approached for this study were selected to reflect the Dutch population based on demographic characteristics that included age, income level, education level, and place of residence. Participation in FlyCatcher surveys is voluntary.

2.2 | Procedures

This survey study was conducted between February and April 2018 in the Netherlands. The surveys were administered via an online survey system; SurveyMonkey was used for the patient sample survey, and FlyCatcher's self-developed survey system was used for the general population sample (FlyCatcher, 2019; Survey Monkey Inc. 2019). Participants recruited via relevant patient organizations were invited by e-mail or by a link on the website or social media of relevant patient organizations. Participants recruited through the online commercial panel gave consent to participate in several surveys about health issues. These participants received a monetary incentive for completing the survey. Participants received an e-mail with a link to the survey. Prior to entering the online survey, information about the aims of the study, the study design, and contact details of the investigators were provided. Entering the online survey was considered as providing informed consent. Participants could exit the survey at any time. Participation was anonymous, and no personal data were collected.

To ensure that participants fulfilled the inclusion criteria, they were first asked whether they had a hereditary disease themselves or in their family. For the patient survey, participants who indicated they had an autosomal recessive or X-linked disease themselves or in their family, or did not have any hereditary disease in their family, were excluded. For the general population survey, participants who indicated they had a hereditary disease themselves or in their family were excluded.

2.3 | Instrumentation

Different survey arms were designed for the patient versus the population sample. The survey for the patient sample was designed by a psychologist (LvdH), a clinical geneticist (IC), and a policy-worker of the VSOP, Dutch Patient Alliance for Rare and Genetic diseases (DS). LvdH and IC constructed the survey for the population sample. The themes addressed in the surveys were identical and were identified by conducting focus groups with HCPs and interviews with probands and relatives (Van den Heuvel et al., 2019). HCPs, including clinical geneticists, genetic counselors, and psychosocial workers, and representatives of patient organizations were asked to provide input and comments on the survey.

The surveys contained multiple-choice items complemented by open answer items. Sociodemographic factors were assessed using the same items in both surveys, including gender, age, education level (categorized in low, moderate, or high education level), marital status, religion, and parenthood. For the patient sample, participants were also asked about the disease diagnosed in themselves/their family. The surveys addressed the following questions: (a) 'Do people wish to be informed about genetic risks?'; (b) 'Which relatives should be informed?'; (c) 'Who should inform at-risk relatives?'; (d) 'How should information for relatives be provided?'; and (e) 'How should ethical issues be handled, such as whether direct contact by HCPs with at-risk relatives without consent of the proband would be justified, and whether contact details of at-risk relatives can be requested from the population register?' Patients and relatives were additionally asked about their opinions regarding the experienced support and follow-up contact by the clinical genetic centers.

The population sample was asked the same questions, but vignettes were included to inform them about hereditary diseases, inheritance pattern, and possible preventive or treatment and reproductive options, with the first vignette describing a case of hereditary breast and ovarian cancer (i.e., in the vignette considered a treatable condition) and the second describing a case of hereditary Alzheimer's disease (i.e., considered an untreatable condition). For the patient sample, participants themselves indicated which disease was diagnosed in themselves/their family, and these diseases were categorized by clinical geneticists as 'treatable' (prevention or treatment of the disease is possible) or 'untreatable' (prevention or treatment of the disease is not possible). English translations of the surveys are shown in Supplementary Material S2.

2.4 | Data analysis

Frequency and descriptive statistics were used to describe the sociodemographic and clinical characteristics of the study sample and the responses on each survey item. Differences between sociodemographic and clinical factors were assessed using chi-square tests (all categorical variables). Chi-square or Fisher's exact tests were also used to assess differences in sociodemographic and clinical factors with regard to responses on survey items. A Freeman–Halton extension of the Fisher exact test was used in case more than 20% of cells had expected count <5. A Bonferroni-corrected two-sided p-value of <.05 was considered significant. Effect sizes were reported in the form of Cramer's V's (described in the results as V), with Cramer's $V < 0.20$ considered as a weak relationship, 0.20–0.30 as a moderate relationship, and >0.30 as a strong relationship. SPSS version 24 was used to perform statistical analyses (IBM Corporation, 2016). LvdH conducted thematic coding analysis on open answers (Braun & Clarke, 2006). Based on coding analysis, a codebook was developed with which themes and subthemes were derived. Analysis of open answers was used to supplement the data.

TABLE 1 Sociodemographic and clinical characteristics

	General population		Probands and relatives
	Responders *N* (%)	Non-responders *N* (%)	Responders *N* (%)
Gender[a]			
Female	522 (52.2)	614 (49.3)	300 (79.2)
Male	478 (47.8)	632 (50.7)	79 (20.8)
Age[a]			
18–24 years	83 (8.3)	148 (11.9)	20 (5.3)
25–34 years	157 (15.7)	233 (18.7)	41 (10.8)
35–44 years	134 (13.4)	231 (18.5)	79 (20.8)
45–54 years	171 (17.1)	276 (22.2)	102 (26.9)
55–64 years	188 (18.8)	153 (12.3)	84 (22.2)
≥ 65 years	267 (26.7)	205 (16.5)	53 (14.0)
Education level[a,b]			
Low	311 (31.1)	310 (24.9)	25 (6.5)
Moderate	398 (39.8)	543 (43.6)	186 (49.1)
High	291 (29.1)	393 (31.5)	159 (41.9)
Children[a]			
Yes	620 (62.6)	719 (57.7)	274 (72.3)
No	370 (37.4)	508 (40.8)	105 (27.7)
Unknown	10 (0.01)	19 (1.5)	0 (0.0)
Religious			
Yes	359 (35.9)	Unknown	129 (34.0)
No	641 (64.1)	Unknown	250 (66.0)

[a]Significant difference between responders in general population and patient sample.

[b]Education level: low = elementary school, lower level of secondary school, lower vocational training; medium = higher level of secondary school, intermediate vocational training; high = higher vocational training, university.

3 | RESULTS

3.1 | Response rate and demographics

In total, 1,379 participants completed the survey: 1,000 participants from the general population and 379 participants from the patient sample. Via the online panel, 3,381 participants from the general population received an e-mail about the survey, and 2,136 responded (response rate 63.2%). Of these, 1,000 met the inclusion criteria of not having a hereditary disease themselves or in the family.

Data of non-responders from the population sample showed significant differences with those of responders on age (people in an older age category more often responded than younger people; $X^2(5) = 69.165$, $p < .001$) and education level (more people with a lower education level responded compared to people with a moderate or high education level; $X^2(2) = 10.740$, $p = .005$). The number of non-responders, and thus the response rate and characteristics of non-responders in the patient sample, is unknown. Because patient organizations used different media to inform patients and relatives about this survey study, it is unknown how many were informed about the survey.

Table 1 shows sociodemographic and clinical characteristics of our samples. Respondents from the patient sample were more likely to be female ($X^2(1) = 109.896$, $p < .001$), to have a moderate or high education level ($X^2(2) = 88.026$, $p < .001$), to have children ($X^2(2) = 11.309$, $p = .001$), and to be middle-aged ($X^2(5) = 51.881$, $p < .001$).

3.2 | Do people wish to be informed about their genetic risks?

Table 2 shows participants' answers on the survey items. The population sample was asked whether they wished to be informed about genetic risks. Most participants indicated they were interested in knowing whether they were at risk of an autosomal dominant disease. This was the case for both treatable conditions and untreatable conditions, although the proportions were significantly different with a moderate effect size ($X^2(1) = 54.327$, $p < .001$, $V = 0.243$). The remaining participants indicated in an open answer that they would not want to receive this information. Others responded that this depends on disease characteristics, individual characteristics of relatives (i.e., age, personal circumstances), closeness of relatives, and/or whether the proband would be able to inform relatives. Chi-square analysis only showed nonsignificant or weak significant associations in sociodemographic characteristics (see Table 3).

3.3 | Which relatives should be informed?

A majority of participants from the patient and population sample indicated that relatives should be informed following the principles of a cascade screening approach (i.e., only first-degree relatives at first, subsequently second- and further-degree relatives; see Table 2). Other options were to inform only first-degree relatives and to inform both first- and further-degree relatives at the same time. More participants from the population sample preferred to inform only first-degree relatives, in contrast to more participants of the patient sample preferring to inform first- and further-degree relatives at the same time. In the patient sample, only a very small minority opted for not informing relatives at all (see Table 2). With regard to sociodemographic characteristics, participants from the patient sample without children more often opted for informing relatives following the principles of cascade screening ($X^2(3) = 13.632$, $p = .003$, $V = 0.201$). Other characteristics showed nonsignificant or weak significant differences in both samples (see Table 3).

TABLE 2 Participants' answers on survey-items

Do you prefer to be informed about genetic risks?	**General population sample, *N* (%)**		**Patient sample, *N* (%)[a]**		
	Treatable condition[b]	Untreatable condition	Treatable condition	Untreatable condition	Total
Yes, always	959 (95.9)	800 (80.0)	NA	NA	NA
No, never	21 (2.1)	123 (12.3)			
Other[c]	20 (2.0)	77 (7.7)			
Which relatives should be informed?	**In both treatable and untreatable conditions**		**In both treatable and untreatable conditions**		
At first first-degree relatives, after hereditary predisposition in a close relative has been established further relatives	531 (53.1)		180 (53.6)		
Only first-degree relatives of the person with the hereditary disease	332 (33.2)		64 (19.0)		
First-degree relatives and other relatives at the same time	137 (13.7)		84 (25.0)		
No relatives	–		8 (2.4)		
Who should inform at-risk relatives?	**Treatable condition[c]**	**Untreatable condition**	**Treatable condition[d]**	**Untreatable condition**	**Total**
By someone in the family or by a HCP	549 (54.9)	513 (51.3)	124 (46.1)	29 (48.3)	153 (46.5)
By someone in the family, not by a HCP	214 (21.4)	242 (24.2)	33 (12.3)	8 (13.3)	41 (12.5)
By a HCP	231 (23.1)	208 (20.8)	13 (4.8)	0 (0.0)	13 (3.9)
At first by someone in the family, subsequently always by a HCP	–	–	94 (34.9)	22 (36.7)	116 (35.3)
Other[b]	6 (0.6)	37 (3.7)	5 (1.9)	1 (1.7)	6 (1.8)
How should at-risk relatives be informed?					
How should information for relatives be provided?	**In both treatable and untreatable conditions**		**In both treatable and untreatable conditions**		
At first limited information with possibility to gain more information	542 (54.2)		285 (90.2)		
All information should be provided at once	457 (45.7)		31 (9.8)		
Other[b]	1 (0.1)		–		
How would you like to be informed?	**Family-mediated approach**	**Direct contact approach**	**In both cases**		
Face-to-face	923 (92.3)	820 (82.0)	132 (43.7)		
By phone	25 (2.5)	64 (6.4)	3 (1.0)		
By letter	22 (2.2)	80 (8.0)	40 (13.2)		
By e-mail	12 (1.2)	21 (2.1)	3 (1.0)		
A combination of methods	–	–	103 (34.1)		
Other	18 (1.8)	15 (1.5)	21 (7.0)		
Should support with informing at-risk relatives be offered?			**In both treatable and untreatable conditions**		
Yes	NA		257 (86.5)		
No			40 (13.5)		
When should support with informing at-risk relatives be offered?			**In both treatable and untreatable conditions**		
Always	NA		128 (50.0)		
Only if patients asks for it			86 (33.6)		
Only if the genetic counselor believes that there is a need for support			31 (12.1)		
Other			11 (4.3)		

(Continues)

TABLE 2 (Continued)

Do you prefer to be informed about genetic risks?	General population sample, *N* (%)		Patient sample, *N* (%)[a]		
Should genetic counselors contact probands after some time?			**In both treatable and untreatable conditions**		
Yes, a few weeks after the test result	NA		120 (40.7)		
Yes, a few months after the test result			48 (16.3)		
Yes, 6 months after the test result			14 (4.7)		
Yes, a year after the test result			5 (1.7)		
Yes, multiple times			39 (13.2)		
No			44 (14.9)		
Other[b]	–		25 (8.5)		
How should ethical issues be handled?					
May contact details of relatives be looked up by HCPs in population registers?	**Treatable condition**	**Untreatable condition**	**Treatable condition**	**Untreatable condition**	**Total**
Yes, this should be allowed	511 (51.1)	496 (49.6)	120 (45.6)	25 (43.9)	145 (45.3)
Yes, this should be allowed and this should also be done	391 (39.1)	391 (39.1)	106 (40.3)	14 (24.6)	120 (37.5)
No, this should not be allowed	81 (8.1)	94 (9.4)	37 (14.1)	18 (31.5)	55 (17.2)
Other[b]	17 (1.7)	19 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Should children of relatives deciding not to have predictive DNA testing be informed?	**In both treatable and untreatable conditions**		**In both treatable and untreatable conditions**		
Yes, they should be informed	631 (63.1)		195 (58.7)		
Dependent on age of children/disease characteristics	247 (24.7)		122 (36.8)		
No, this should not be allowed	76 (7.6)		15 (4.5)		
Other[b]	46 (4.6)		0 (0.0)		
Should relatives be directly informed by HCPs if the proband is unwilling to inform?	**Treatable condition[c]**	**Untreatable condition**	**Treatable condition[d]**	**Untreatable condition**	**Total**
Yes, HCPs should inform relatives directly in this case	607 (60.7)	653 (65.3)	122 (46.0)	15 (25.9)	137 (42.4)
No, HCPs should not inform relatives directly	289 (28.9)	283 (28.3)	41 (15.5)	21 (36.2)	62 (19.2)
Other[b]	104 (10.4)	64 (6.4)	102 (38.5)	22 (37.9)	124 (38.4)

Note: NA not applicable, survey item or response item is not included in the survey

[a]Not all numbers add up to the total number of patient sample participants due to missing data. For the patient sample, participants themselves indicated which disease was diagnosed in themselves/their family, and these diseases were categorized by clinical geneticists as: (a) treatable: prevention or treatment of the disease is possible, or (b) untreatable: prevention or treatment of the disease is not possible.

[b]Other: open answer options are explained in the text

[c]Considered significant based on the Bonferroni-adjusted *p*-level of $p < .010$ (0.05/5).

[d]Considered significant based on the Bonferroni-adjusted *p*-level of $p < .008$ (0.05/6). Open answer categories were not included in the chi-square analysis due to the small numbers resulting in the chi-square analyses being not appropriate.

3.4 | Who should inform at-risk relatives?

Table 2 describes the responses in case of a treatable or untreatable condition (both for the population and for the patient sample). A large proportion of participants from the patient and the population sample believed that someone in the family and/or HCPs should inform at-risk relatives. Many participants from the patient sample also believed that at first someone in the family could inform relatives and that subsequently the HCP should always inform relatives (as well). A majority (62.5%) of these participants indicating that the HCP should be involved in informing at-risk relatives believed that the genetic counselor or clinical geneticist would be the most suitable person to do this. Some also considered the medical specialist (21.5%) or general practitioner (9.7%) a possibility. The remaining participants from both samples reported that only the proband or someone else in the family should inform at-risk relatives or that only the HCP should inform at-risk relatives. Some participants from the patient sample mentioned that this depends on the condition

TABLE 3 Chi-square tests of differences between sociodemographic and clinical variables per survey item

Do you wish to be informed about genetic risks?	General population sample						Patient sample		
	Treatable condition			Untreatable condition			In both treatable and untreatable conditions		
Preferred to be informed	*N* (%)	*p*	Effect size (*V*)[d]	*N* (%)	*p*	Effect size (*V*)	*N* (%)	*p*	Effect size (*V*)
Gender									
Males	495 (96.7)	.008[a]	Weak	423 (86.0)	.560	Weak	NA		
Females	464 (99.1)			377 (87.5)					
Education level									
Low	293 (30.6)	.031	Weak	249 (31.1)	.142	Weak	NA		
Moderate	389 (40.6)			333 (41.6)					
High	277 (28.9)			218 (27.3)					
Parenthood[e]									
Yes	596 (97.4)	.257	Weak	504 (87.3)	.423	Weak	NA		
No	353 (98.6)			289 (85.5)					
Religion									
Yes	340 (96.9)	.114	Weak	283 (84.2)	.107	Weak	NA		
No	619 (98.4)			517 (88.1)					

Which relatives should be informed?	In both treatable and untreatable conditions			In both treatable and untreatable conditions		
At first first-degree relatives, subsequently further-degree relatives	*N* (%)	*p*	Effect size (*V*)	*N* (%)	*p*	Effect size (*V*)
Gender						
Males	254 (48.7)	.001[a]	Weak	36 (49.3)	.045	Weak
Females	277 (57.9)			144 (54.8)		
Education level						
Low	137 (44.1)	<.001[a]	Weak	12 (54.5)	.721	Weak
Moderate	200 (50.3)			89 (53.6)		
High	194 (66.7)			79 (53.4)		
Parenthood[e]						
Yes	317 (51.1)	.378	Weak	124 (51.0)	.003[c]	Moderate
No	206 (55.7)			56 (60.2)		
Religion						
Yes	189 (52.6)	.121	Weak	62 (54.4)	.151	Weak
No	342 (53.4)			118 (53.2)		
Patient type						
Affected	NA			121 (53.5)	.196	Weak
Carrier				32 (50.0)		
Non-carrier				27 (58.7)		

Who should inform at-risk relatives?	Treatable condition			Untreatable condition			In both treatable and untreatable conditions		
By proband and/or HCP	*N* (%)	*p*	Effect size (*V*)	*N* (%)	*p*	Effect size (*V*)	*N* (%)	*p*	Effect size (*V*)
Gender									
Males	263 (52.1)	<.001[a]	Weak	247 (48.1)	<.001[b]	Weak	34 (48.6)	.244	Weak

(Continues)

TABLE 3 (Continued)

Who should inform at-risk relatives?	Treatable condition			Untreatable condition			In both treatable and untreatable conditions		
By proband and/or HCP	*N* (%)	*p*	Effect size (*V*)	*N* (%)	*p*	Effect size (*V*)	*N* (%)	*p*	Effect size (*V*)
Females	286 (47.9)			266 (57.5)			119 (47.0)		
Education level									
Low	172 (55.3)	.001[a]	Weak	166 (56.3)	.001[b]	Weak	10 (45.5)	.525	Weak
Moderate	228 (57.3)			216 (56.1)			67 (42.4)		
High	149 (51.2)			131 (46.3)			76 (53.1)		
Parenthood[e]									
Yes	347 (56.3)	.545	Weak	314 (53.0)	.929	Weak	98 (42.1)	.014	Weak
No	200 (54.3)			196 (54.3)			55 (61.1)		
Religion									
Yes	187 (52.2)	.096	Weak	172 (50.1)	.008[b]	Weak	46 (41.4)	.165	Weak
No	362 (56.9)			341 (55.0)			107 (50.5)		
Patient type									
Affected	NA			NA			94 (43.4)	.280	Weak
Carrier							36 (58.1)		
Non-carrier							23 (52.3)		

How should ethical issues be handled?	Treatable condition			Untreatable condition			In both treatable and untreatable conditions		
Contact details of relatives may be looked up by HCPs in registers	*N* (%)	*p*	Effect size (*V*)	*N* (%)	*p*	Effect size (*V*)	*N* (%)	*p*	Effect size (*V*)
Gender									
Males	263 (51.1)	.547	Weak	237 (46.1)	.008[b]	Weak	29 (42.6)	.487	Weak
Females	248 (53.0)			259 (55.5)			116 (46.0)		
Education level									
Low	178 (58.0)	.110	Weak	158 (51.5)	.002[b]	Weak	8 (38.1)	.881	Weak
Moderate	199 (51.0)			198 (50.5)			76 (48.1)		
High	134 (46.9)			140 (49.6)			61 (43.3)		
Parenthood[e]									
Yes	332 (54.5)	.003[a]	Weak	301 (49.5)	.002[b]	Weak	102 (44.0)	.427	Weak
No	176 (48.2)			190 (52.3)			43 (48.9)		
Religion									
Yes	204 (58.1)	.013	Weak	184 (52.4)	.561	Weak	47 (43.5)	.864	Weak
No	307 (48.6)			312 (49.5)			98 (46.2)		
Patient type									
Affected	NA			NA			95 (44.6)	.052	Weak
Carrier							26 (41.3)		
Non-carrier							24 (54.5)		

(Continues)

TABLE 3 (Continued)

Children of relatives who decide against predictive DNA testing should be informed	In both treatable and untreatable conditions			In both treatable and untreatable conditions		
	N (%)	*p*	Effect size (*V*)	*N* (%)	*p*	Effect size (*V*)
Gender						
Males	335 (67.4)	.002[a]	Weak	34 (47.9)	.048	Weak
Females	296 (64.8)			161 (61.7)		
Education level						
Low	218 (72.7)	.006[a]	Weak	15 (68.2)	.094	Weak
Moderate	253 (66.4)			99 (60.7)		
High	160 (58.6)			81 (55.1)		
Parenthood[e]						
Yes	386 (65.6)	.790	Weak	148 (61.9)	.137	Weak
No	241 (67.6)			47 (50.5)		
Religion						
Yes	227 (66.4)	.953	Weak	63 (55.8)	.697	Weak
No	404 (66.0)			132 (60.3)		
Patient type						
Affected	NA			133 (59.6)	.136	Weak
Carrier				35 (54.7)		
Non-carrier				27 (60.0)		

Relatives should be directly informed when proband does not inform them	Treatable condition			Untreatable condition			In both treatable and untreatable conditions		
	N (%)	*p*	Effect size (*V*)	*N* (%)	*p*	Effect size (*V*)	*N* (%)	*p*	Effect size (*V*)
Gender									
Males	301 (57.7)	<.001[a]	Weak	328 (62.8)	.023	0.087	25 (36.2)	.065	Weak
Females	306 (64.0)			325 (68.0)			112 (44.1)		
Education level									
Low	176 (56.6)	.021	Weak	211 (678)	.386	0.046	7 (31.8)	.520	Weak
Moderate	257 (64.6)			265 (66.6)			69 (43.7)		
High	174 (59.8)			177 (60.8)			61 (42.7)		
Parenthood[e]									
Yes	365 (58.9)	.174	Weak	404 (65.2)	.967	0.008	102 (43.6)	.298	Weak
No	236 (63.8)			243 (65.7)			35 (39.3)		
Religion									
Yes	198 (55.2)	.011	Weak	219 (61.0)	.073	0.072	40 (36.4)	.089	Weak
No	409 (63.8)			434 (67.7)			97 (45.5)		
Patient type									
Affected	NA			NA			77 (35.8)	.005[c]	Weak
Carrier							37 (58.7)		

(Continues)

TABLE 3 (Continued)

Relatives should be directly informed when proband does not inform them	Treatable condition			Untreatable condition			In both treatable and untreatable conditions		
	N (%)	*p*	Effect size (*V*)	*N* (%)	*p*	Effect size (*V*)	*N* (%)	*p*	Effect size (*V*)
Non-carrier							23 (51.1)		

Note: NA, not applicable, survey item not included in the survey, or comparison of treatable and untreatable conditions; *N* (%): percentage within category

[a]Considered significant based on the Bonferroni-adjusted *p*-level of $p < .010$ (0.05/5)

[b]considered significant based on the Bonferroni-adjusted *p*-level of $p < .013$ (0.05/4)

[c]considered significant based on the Bonferroni-adjusted *p*-level of $p < .008$ (0.05/6). Open answer categories were not included in the chi-square analysis due to the small numbers resulting in the chi-square analyses being not appropriate.

[d]Effect size using Cramer's *V*: weak effect size = Cramer's $V < 0.20$; moderate effect size = Cramer's $V = 0.20–0.30$; strong effect size = Cramer's $V > 0.30$

[e]Due to missing values regarding parenthood (unknown: $N = 10$) in the general population sample, the total numbers differ from Table 2.

involved. As shown in Table 3, a significant difference with moderate effect size was observed between attitudes in case of a treatable or untreatable disease in the population sample, although again no clear direction of the difference could be identified ($X^2(4) = 624.261$, $p < .001$, $V = 0.243$). Only nonsignificant or weak associations in sociodemographic factors were shown.

3.5 | How should information for at-risk relatives be provided?

3.5.1 | Stepwise information provision

Almost all participants from the patient sample believed that the first information provided to relatives should be concise, with the possibility to receive more information (see Table 2). Only a small minority held the opinion that all available information should be handed over at once. In contrast, almost half of participants from the population sample believed that all information should be provided at the same time. The other half believed that at first limited information should be provided with the possibility to gain more information. One participant from the population sample reported to be unsure.

3.5.2 | Medium used to inform relatives

As shown in Table 2, many participants from the population and the patient sample preferred to inform relatives in a personal manner (i.e., face-to-face). Other participants from both samples preferred information provided by telephone, letter, or e-mail. The remainder filled out the open answer option, all answering that the type of medium used would depend on the closeness of relatives.

3.5.3 | Support by HCPs

The patient sample was additionally asked for their opinion regarding support offered by HCPs in general. A majority of participants believed support should be offered by HCPs, with half believing this should always be offered. Others believed that this should only be done if patients ask for it, that this should only be offered when the HCP thinks that support is needed, or that this depends on the situation (see Table 2). In addition, a majority of patients and relatives preferred follow-up contact by their genetic counselor. A large proportion believed that genetic counselors should ideally do this a few weeks after receiving the test result. Others believed that this should be done a couple of months after receiving the test result or that patients should be contacted multiple times after receiving the test result.

3.6 | How should ethical issues be handled?

3.6.1 | Contact details of relatives in population registers

In clinical genetic practice, one sometimes encounters that probands do not have any contact details of at-risk relatives and therefore cannot inform relatives. In this situation, a large proportion of participants from both samples believed clinical genetic practices should be allowed to look up contact details of relatives in population registers (see Table 2). An additional 39.1% of the population participants (in case of both treatable and untreatable disease) and 37.5% of patients and relatives thought this should even be obligatory.

Preferences in the population sample differed significantly for treatable versus untreatable conditions showing a strong effect size, although no clear direction of the difference was observed ($X^2(4) = 826.710$, $p < .001$, $V = 0.652$; see Table 3). In both samples, only nonsignificant or weak significant associations were shown in other factors.

3.6.2 | Informing children of relatives who decide not to have predictive DNA testing

In both the patient sample and the population sample, more than half of participants believed that the children of relatives who decide not to get tested should be informed (see Table 2). Some participants believed this depends on the age of children, whether preventive or treatment options are available, and whether there are reproductive possibilities. A few participants gave an open answer that this is the responsibility of parents. Some did not elaborate on their opinion but considered this an ethical dilemma (see Table 2). As shown in Table 3, chi-square analysis showed only nonsignificant or weak significant associations in sociodemographic and clinical characteristics in both samples.

3.6.3 | Directly informing relatives by HCPs when the proband prefers not to inform relatives

Participants were also asked whether at-risk relatives should be informed if the proband is unwilling to. A large proportion of the patient sample believed that HCPs should inform relatives in this case. A larger percentage of participants of the population sample shared this opinion. This was the case in treatable and untreatable conditions, although a significant difference with a strong effect size was found ($X^2(4) = 572.868$, $p < .001$, $V = 0.535$). Also, a large proportion of the patient sample filled out the open answer option, indicating that they believed this depended on whether there were preventive or treatment options or reproductive options, and/or, in case of minors, the age of relatives (see Table 2). Participants with an untreatable hereditary disease themselves or in their family more often believed relatives should not be informed when the proband is unwilling to inform, showing a moderate association ($X^2(2) = 15.229$, $p < .001$, $V = 0.217$). Only nonsignificant or weak associations were found in the patient sample.

4 | DISCUSSION

In the present study, we have assessed the preferences of Dutch probands and relatives, and members of the general population on how to inform at-risk relatives of autosomal dominant diseases. Our findings show that many participants preferred that the proband informs at-risk relatives. However, a majority believed HCPs should also be involved in this information process. There was an agreement between the patient and population sample on this matter. Previous research also indicated that patients and relatives often prefer the proband to inform relatives, because this seems the most logical approach (Forrest et al., 2003; Keenan et al., 2005; Leenen et al., 2016; Pentz et al., 2005).

Active involvement of HCPs was, however, desired by both our patient and population sample. Our findings indicate that HCPs should primarily engage in a supportive role, supporting probands in informing at-risk relatives by providing information and providing help if probands are unable or unwilling to inform relatives. Some participants were in favor of direct contact by HCPs in all cases. Interestingly, a majority of participants from the general population preferred relatives to be informed personally, in case of both a family-mediated and a direct contact approach. This suggests that personal contact between relatives and HCPs might be considered beneficial, including when using a direct contact approach.

Most participants preferred the principles of a cascade screening approach. This is also the most logical approach from a healthcare perspective, since relatives with the highest risk are approached at first (Miller et al., 2013). In addition, psychological harm for second-degree relatives with a connecting first-degree relative who does not have the genetic predisposition can be prevented (Miller et al., 2013; Van Langen, Hofman, Tan, & Wilde, 2004). However, previous studies suggest that the process of cascade screening often breaks down and further-degree relatives are not reached (Burns et al., 2016; Shah et al., 2018). Interestingly, a majority of participants in our study believed that in case a relative decides to not get tested, connecting second-degree relatives should be informed.

Our findings show that information material for relatives provided by HCPs was generally desired. Previous studies suggested that educational material should be provided in a stepwise manner, with only limited information at first (Ratnayake et al., 2011; Van den Nieuwenhoff, Mesters, Nellissen, Stalenhoef, & de Vries, 2006). In the present study, a majority of participants from the patient sample also preferred to receive information in a stepwise manner. Almost all members of the general population participating in this study, however, believed all available information for relatives should be provided at once. This difference might be explained by the fact that patients and relatives have experienced the process of informing at-risk relatives, while it remains a hypothetical situation for members of the general population.

We additionally explored what participants believed about handling situations where ethical issues are at stake. In current practice, clinical genetic practice relies on the proband to inform at-risk relatives, thereby retaining patient confidentiality and relatives' right not to know. These ethical principles are, however, also at stake when patients share with their genetic HCP that they do not intend to inform at-risk relatives. Importantly, a majority of participants believed that HCPs should directly contact relatives in cases where the proband is unwilling to inform at-risk relatives. Furthermore, a majority believed that clinical genetic centers should be allowed to use population registers to retrieve contact details of at-risk relatives, if unavailable via the proband. The possibility to become aware of genetic risks therefore seems to be an important issue for a majority of probands, relatives, and the general population (Petersen et al., 2019; Sermijn et al., 2016). In treatable conditions, the 'right to know' might be considered more important than patient confidentiality, as indicated in a previous qualitative study in the Netherlands (Van den Heuvel et al., 2019).

This was also felt by HCPs, as they feel a responsibility not to harm relatives by leaving them unaware of their genetic risk (Van den Heuvel et al., 2019).

Attitudes toward informing relatives in case of treatable versus untreatable hereditary conditions were assessed as well. Although the majority of both samples was in favor of informing relatives in both treatable and untreatable hereditary conditions, some differences were observed. As can be hypothesized, the availability of prevention and treatment options seemed to influence preferences regarding how relatives should be informed, with participants being more inclined to believe that relatives should be informed in cases of treatable hereditary conditions. In the patient sample, this was primarily observed in preferences regarding ethical issues. In the population sample, significant differences were observed on quite a few survey items, although no clear direction of the difference could be observed and associations were often weak. This can be explained by the large sample size, which may lead to small differences being statistically significant. Furthermore, the population sample was asked to consider a hypothetical situation of being at risk for a treatable and untreatable condition, while the patient sample was asked to fill out the survey based on their own disease.

4.1 | Implications for clinical practice

As illustrated by Burns et al. (2018), informing relatives is a complex process that requires the proband to be able to correctly convey the information and relatives to understand the information and connect this to appropriate services. Current clinical genetic practice may be insufficient considering the low uptake of genetic counseling. Our findings suggest that there is a need for other approaches with a more active role of HCPs to provide sufficient support for probands in informing at-risk relatives of autosomal dominant diseases. The field of genetic counseling may therefore consider ways to actively support the proband in informing relatives, for example, by providing a family letter and educational material. This educational material should contain information not only on the familial disease, but also on what probands can encounter when informing relatives. Furthermore, follow-up contacts by HCPs with probands and relatives with the genetic predisposition regarding informing at-risk relatives should be incorporated in this approach to facilitate the information process. As stated by Schwiter et al. (2018), cascade testing should not be a one-time conversation. One could, however, imagine that a more active role of HCPs in informing at-risk relatives may also have downsides, such as higher workload or less time to see other patients. Furthermore, time spent on relatives who are not registered as patients yet cannot be billed.

The findings of this study contribute to our understanding of patient attitudes toward the approach used to inform at-risk relatives. Moreover, to our knowledge, little was known on preferences of the general population prior to this study. The current findings are particularly important as the general population includes individuals who may be informed about a genetic disease risk in the future. Our findings suggest that the views of the general population generally corresponded with the views of patients and relatives. Regarding uptake of genetic counseling, a direct contact approach seems to be the most optimal (Aktan-Collan et al., 2007; Sermijn et al., 2016; Suthers et al., 2006). Our findings, however, indicate that participants prefer both patients and HCPs to be involved in informing at-risk relatives and not solely HCPs. To be effective in clinical genetic practice, it is essential that the approach used to inform at-risk relatives is acceptable and feasible for all stakeholders. Further research is therefore needed to compare other more active approaches incorporating these preferences, ideally using intervention studies.

4.2 | Limitations

This study had several limitations. Since only Dutch participants were included in the survey, these results cannot be generalized to other populations. Besides, the patient sample and population sample survey were slightly different and significant differences between both samples in sociodemographic characteristics were observed. The patient sample included in this survey study was also smaller than the population sample. For these reasons, comparison of both surveys was not optimal. Furthermore, the surveys for the patient sample and population sample were not piloted, thereby potentially administering unclear questions.

Unfortunately, it was not possible to determine a response rate in patients and relatives. In addition, a response bias in patients and relatives could be present. Patients who experienced problems in informing at-risk relatives were possibly more inclined to participate. However, having negative experiences with informing at-risk relatives may also have caused patients to not participate in the survey. Relatives who had a positive attitude to being informed about the hereditary disease in their family were probably also more inclined to participate than relatives who did not. The comparison of responders and non-responders of the general population sample showed significant differences in age and education level, indicating a response bias in this sample as well. The high rate of participants in the population survey indicating to have a genetic disease also indicates that there was a bias in people signing up for the FlyCatcher research surveys. However, a genetic disease in the family can be interpreted in a broad sense, including Down syndrome in a fourth-degree relative. This general exclusion criterion resulted in participants that are unaware of a genetic disease in their family, which is what we aimed for.

5 | CONCLUSIONS

This survey study on preferences regarding informing at-risk relatives of autosomal dominant diseases showed that a majority of Dutch patients and relatives, as well as Dutch members of the general population, generally felt that both the proband and the HCP

should be involved in informing relatives at risk of autosomal dominant diseases. Support of HCPs was, however, desired, including the provision of educational material for relatives and follow-up contacts with the proband. Breaching patient confidentiality was considered an ethical issue, although most participants believed informing at-risk relatives was more important. Incorporating these preferences into the approach used to inform at-risk relatives may increase the number of (adequately) informed relatives, and therefore enable more at-risk relatives to make an informed decision regarding predictive DNA testing. Further research, specifically intervention studies, on novel approaches incorporating these preferences to inform at-risk relatives of autosomal dominant diseases is needed.

AUTHOR CONTRIBUTIONS

LvdH, DS, and IC designed the surveys. LvdH was involved in drafting the manuscript. DS, WvZS, FW, and IC critically revised the manuscript. All authors were involved in the final approval of the manuscript.

ACKNOWLEDGEMENTS

We acknowledge the members of the guideline committee and the patient advisory board for their input on the survey. We also thank the study participants for participating in this survey study.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest

LvdH, DS, WvZS, FW, and IC declare they have no competing interests.

Human studies and informed consent

This study did not meet the criteria for review by a Medical Ethical Committee. Information about the survey was provided to participants prior to entering the survey. Entering the survey was considered informed consent.

Animal studies

This article does not contain any studies with animals performed by any of the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Marleen van den Heuvel L, Stemkens D, van Zelst-Stams WAG, Willeboordse F, Christiaans I. How to inform at-risk relatives? Attitudes of 1379 Dutch patients, relatives, and members of the general population. *J Genet Couns*. 2019;00:1–14. https://doi.org/10.1002/jgc4.1206